REMARKS

Claims 1-4, 6, 9, 11, 12, 14-25, 27, 29, and 31-64 are pending in this application. Claims 3, 4, 11, 12, 20-25, 27, 29, and 31-64 have been withdrawn from consideration and canceled. Claims 1, 2, 6, 9, and 14-19 have been rejected. Claims 1, 6, 18 and 19 have been amended. Claims 2, 9, and 14-16 have been canceled. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Election/Restriction Requirement Under 35 U.S.C. §121

The restriction requirement placing the claims into Groups I-VIII has been deemed proper and made final. Claims 3, 4, 11, 12, 20-25, 27, 29, and 31-64 have been withdrawn from further consideration. Accordingly, Applicant is canceling the withdrawn claims without prejudice, reserving the right to file continuing applications for the canceled subject matter.

II. Priority

Priority to U.S. Provisional Patent Application Serial No. 60/261,252, filed January 12, 2001 has been acknowledged by the Examiner, however, claims 9 and 15 of the instant application have been suggested to lack support in the provisional application and are therefore considered to have an effective filing date of instant application, *i.e.*, January 11, 2002. In an effort to facilitate prosecution of the instant application, Applicant has canceled claims 9 and 15.

III. Objection to Amendment

The amendment filed June 25, 2002 has been objected to under 35 U.S.C. § 132(a) because it introduces new matter to the disclosure. To comply with the duty of disclosure under 37 C.F.R. 1.56, Applicant submitted the amendment to disclose that the BMP-2 primers used in the RT-PCR analysis of paragraph [**0089**] were potentially capable of amplifying both BMP-2 and BMP-4. The Examiner suggests that this disclosure constitutes new matter because the application did not reveal the fact that primers used to amplify nucleic acid encoding BMP-2 were not specific. To facilitate the prosecution of the instant application, Applicant has amended paragraph [**0089**] of the original disclosure, removing reference to the subject matter added by amendment on June 25, 2002. Withdrawal of this objection is therefore respectfully requested.

IV. Objection to the Specification

The specification is objected to for failing to provide proper antecedent basis for the claimed subject matter. It is suggested that while claim 9 recites, "wherein the bone morphogenetic-2 activity inhibitor is a polypeptide the amino acid sequence of which comprises at least ten consecutive amino acids of noggin", the claim language finds no antecedent basis in the originally filed disclosure. In view of Applicant's cancellation of claim 9 above, this objection is moot. Withdrawal of this objection is therefore respectfully requested.

The specification has also been objected to for failing to demarcate trademarks such as GenBank™, Pharmacia™, ABI Prism™, and Tween™; for misspelling "ABI Prism™" as "IBI Prism™" at page

37; and for mistyping "4°C" as "4oC" at page 39. The Examiner has required appropriate correction. Applicant has amended the specification to include trademarks and correct inadvertent typographical errors, where appropriate. Withdrawal of these objections is therefore respectfully requested.

V. Objection to the Claims

Claim 18 has been objected to because bone morphogenetic protein-2 activity inhibitors are compounds which do not further comprise a pharmaceutically acceptable carrier.

Claim 19 has been objected to for the inadvertent typographical omission of a comma after "intravenously."

Applicant has made the appropriate corrections to claims 18 and 19. Withdrawal of these objections is therefore respectfully requested.

VI. Claim rejections under 35 USC §112

Claims 1, 2, 9, and 14-19 have been rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement. It is suggested that the structural and functional variability of the members of the genus of agents that are capable of inhibiting an activity of BMP-2 is evident upon consideration of the disparate structures and functions of the various different types of molecules or compounds that are used in practicing the invention (*e.g.*, antisense oligonucleotide vs. an antibody vs. a ligand of BMP-2). The Examiner suggests that the variability is further evident upon consideration of the disparate structures and functions of the known, naturally occurring inhibitors of the activity of BMP-2 (*e.g.*, noggin,

gremlin, etc.), which do not appear to share at least one structural feature for identifying these proteins. Further, it is suggested that the claims encompass the use of fragments of these naturally occurring proteins, however the specification does not describe which fragments comprising at least ten consecutive amino acids of noggin are capable of inhibiting an activity of BMP-2. The Examiner further suggests that because the claims encompass a genus of substances having the ability to inhibit an activity of BMP-2 to achieve therapeutic effect in the treatment of cancer, which vary both structurally and functionally, an adequate written description must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. Applicant respectfully disagrees with this rejection.

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an Applicant must convey with reasonable clarity to <u>those skilled in the art</u> that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed.

At the time of filing, the structure and function of polypeptides that antagonize the activity of BMP-2 were well-

known in the art. For example, Merino et al. ((1999) *Development* 126:5515-22, enclosed herewith) teach that the DAN family of BMP antagonists, including gremlin and noggin, are a highly conserved family of proteins (see abstract, lines 2-5) that "share the functional property of binding specifically to BMPs, thus preventing their interaction with their receptors" (see page 5516, lines 1-5 of the first full paragraph). Likewise, Hsu et al. ((1998) *Mol. Cell* 1:673-83; abstract enclosed herewith) teach that BMP antagonist Gremlin, Cerberus, and DAN block BMP signaling by binding BMPs, preventing them from interacting with their receptors (see abstract). In this regard, the specification teaches at page 17, lines 10-17, that at the time of filing, polypeptides such as noggin, chordin, gremlin, cerberus 1 homolog, and DAN had defined structures and these proteins were known to share the functional property of binding to BMP-2 thereby preventing activation of the BMP receptor (see page 35, lines 20, to page 36, line 3). The specification further teaches that one representative member of this family of proteins, namely noggin, inhibits tumor growth and vasculature by inhibiting the activity of BMP-2. See page 36, lines 5-13, of the specification. Accordingly, one of ordinary skill in the art would readily appreciate that other known polypeptides which specifically bind BMP-2 and prevent BMP receptor activation would be useful in carrying out the method of the instant invention.

Compliance with written description requirement of 35 U.S.C. § 112, first paragraph, may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. For some biomolecules,

examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. See MPEP §2163.

Accordingly, in an earnest effort to clarify the nature of the claimed compounds, Applicant has amended the claims to indicate that cancer treatment is carried out by administering a polypeptide that binds specifically to a BMP-2 so that BMP-2 receptor activation is prevented thereby treating the cancer. Support for these amendments is found at page 17, lines 10-17, and the paragraph bridging pages 35 and 36. In light of this amendment, claim 2 has been canceled. Applicant believes the teachings of the instant invention conveys with reasonable clarity to those of skill in the art (*e.g.*, Merino et al. and Hsu et al.) that, as of the filing date sought, Applicant was in possession of that which is now claimed. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Claims 1, 2, 6, 9 and 14-19 have been rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. It is suggested that the presumed utility of the claimed invention is largely based upon a disclosure in the specification of an observation that BMP-2 is overexpressed in lung cancer cells, as compared to normal lung cells. The Examiner suggests that in Applicant's amendment filed June 25, 2002, Applicant sought to amend the specification to indicate that the primers used to amplify BMP-2 nucleic acids were

potentially capable of amplifying both BMP-2 and BMP-4 and therefore the underlying premise upon which utility is asserted is amiss and pharmacological inhibition of BMP-2 for treating cancer is questionable. It is further suggested that because proteins such as BMP-2 are multifunctional; the specific activity being inhibited by the members of the claimed genus is not specified nor described in a limiting manner elsewhere in the specification; apart from the procurement of noggin from a commercial source, the production of molecules and compounds used in practicing the claimed invention is not exemplified; fragments of human noggin are not described; and treatment of cancer in a patient is not exemplified, that the instant invention is not enabled. Moreover, the Examiner suggests that the specification only shows that noggin can reduce the growth of lung cancer cells injected subcutaneously in nude mice and the claims are not specifically limited to any one type of cancer.

The Examiner has cited Applicant's own publications, published after the filing date of the instant invention (*i.e.*, 2003 and 2004), as evidence that the specific mechanism activated by BMP-2 in human carcinomas has not been established and therefore, while our understandings of the role of BMP-2 in lung is advancing, it is not complete. Further, it is suggested that because Tada et al. ((1998) *Oncol. Rep.* 5:1137-1140) report treatment of A549 lung cancer cells results in inhibition of growth in anchorage-dependent and independent growth conditions and Buckley et al. ((2004) *Am. J. Physiol. Lung Cell Mol. Physiol.* 286:L81-L86) disclose results that they conclude show that BMP-2 suppresses the transformed phenotype of A549 cells *in vitro*, that the inhibition of BMP-2 would not be therapeutic.

Moreover, it is suggested that the teachings of Hardwick et al. ((2004) *Gastroenterology* 126:111-121); Haramis et al. ((2004) *Science* 303:1684-1686); and Nishanian et al. ((2004) *Biochem. Biophys. Res. Commun.* 323:91-97) indicate that BMP-2 may prevent colon cancer, whereas the teachings of Ghosh-Choudhury et al. ((2000) *Biochem. Biophys. Res. Comm.* 272:705-11); Tomari et al. ((2005) *Int. J. Mol. Med.* 15:253-258); Nakamura et al. ((2003) *Biochem. Biophys. Res. Comm.* 307:206-213) and Wen et al. ((2004) *Biochem. Biophys. Res. Comm.* 316:100-106) indicate that BMP-2 is involved in suppressing growth of breast, prostate, gastric and brain cancer cells, respectively. It is suggested that it is not clear that inhibiting the activity of BMP-2 would be reasonably expected to be therapeutic in the treatment of cancer.

The Examiner further suggests that one cannot extrapolate the teachings of the instant specification to the enablement of the invention, particularly in the absence of exemplification that is commensurate in scope with the claims, because it is well-known that the art of drug discovery is highly unpredictable as evidenced by the teachings of Gura ((1997) *Science* 278:1041-1042) and Bergers et al. ((2000) *Curr. Opin. Genet. Dev.* 10:120-127). It is suggested that the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify "BMP-2 activity inhibitors" that produce the desired therapeutic effect in a patient diagnosed with cancer. Applicant respectfully traverses this rejection.

While Applicant's amendment filed June 25, 2002 was submitted to clarify that primers used to amplify BMP-2 nucleic acids could also potentially amplify BMP-4, Applicant has definitively disclosed at page 31, lines 19-23, that *BMP-2*

protein levels are elevated in tumor samples derived from patients with lung cancer. Applicant further demonstrates at page 34 (lines 7) to page 36 (line 16) that a polypeptide such as noggin, that binds specifically to BMP-2 so that BMP-2 receptor activation is prevented, inhibits tumor growth and vasculature in A549 lung cancer mouse xenografts. Applicant's invention is based upon this insight into the correlation that exists between lung tumor growth *in vivo* and expression of BMP-2. Accordingly, in earnest effort to highlight this correlation, Applicant has amended claim 1 to indicate that the cancer being treated is lung cancer. In light of this amendment, claims 14 and 16 have been canceled.

Regarding the references cited by the Examiner, Hardwick et al.; Haramis et al.; Nishanian et al.; Ghosh-Choudhury et al.; Tomari et al.; Nakamura et al. and Wen et al. teach the BMP-2 in colon, breast, prostate, gastric and brain cancer cells and are silent to BMP-2 in lung cancer. Tada et al. and Buckley et al. teach the effects of BMP-2 on growth of A549 cell *in vitro* with not disclosure as to the effects of BMP-2 *in vivo*. In contrast, Applicant's own publications published in 2003 and 2004 teach *in vivo* lung tumor growth inhibition by BMP-2 antagonists, further supporting the therapeutic endpoint of treating lung cancer using a BMP-2 antagonist.

Applicant respectfully disagrees with the Examiner's suggestion that one of skill in the art could not extrapolate the teachings of the instant specification to the enablement of the invention. The use of human A549 mouse xenografts for evaluating therapeutic efficacy of drugs for treating lung cancer is well-established in the art. For example, Sirotnak et al. ((2000)

Clin. Cancer Res. 6:4885-92; abstract enclosed herewith) teach that co-administration of ZD1839 with cytotoxic agents is highly effective at regressing A549 tumors in mice. In phase I clinical trials with this same drug (*i.e.*, ZD1839), toxicity was manageable and clinical responses were observed in patients with various malignant tumors, in particular non-small cell lung cancer (see Meric et al. (2000) *Bull. Cancer.* 87(12):873-6; abstract enclosed herewith). Thus, in accordance with MPEP 2164.02, Applicant has provided an *in vivo* animal model example in the specification, which one of skill in the art would readily recognize as a working example commensurate in scope with the amended claims.

In addition to a working example, Applicant has provided at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim. MPEP 2164.01(b). For example, the specification teaches at page 17, lines 10-17, various sources for obtaining polypeptides that bind specifically to a BMP-2 protein, and in the alternate, methods for delivering such polypeptides from expression vectors (see page 19, line 5 to page 20, line 20). The paragraph bridging pages 23 and 24, in combination with page 25, lines 4-15, teach formulations and modes of administration of the claimed polypeptides. Page 16, lines 2-14, further discloses that a polypeptide that binds specifically to BMP-2 can be used to treat a cancer such as lung cancer. Thus, in light of the working examples, claim amendments and accompanying remarks which outline one or more methods for making and using the claimed invention, Applicant believes that the enablement requirement of 35 U.S.C. §

112 is satisfied. Reconsideration and withdrawal of this rejection is respectfully requested.

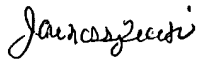
VII. Double Patenting

Claims 1 and 14-19 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 14 of copending Application No. 10/692,824. It is suggested that while the conflicting claims are not identical, they are not patentably distinct from each other. Applicant respectfully requests that this rejection be held in abeyance until allowable subject matter has been identified in copending Application No. 10/692,824.

VIII. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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